REVIEWS

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Direct Oral Anticoagulants in Patients with Thrombophilia: Challenges in Diagnostic Evaluation and Treatment**

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A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article

Abstract

Direct oral anticoagulants (DOACs) or non-vitamin K oral anticoagulants (NOACs) are increasingly used in the prevention of recurrent venous thromboembolism (VTE), including that associated with thrombophilia. The efficacy of DOACs in thrombophilic patients, especially those with severe trombophilia or triple positive antiphospholipid syndrome (APS) with arterial thromboembolic events, remains controversial. Most case reports and case series indicate that DOACs are an attractive therapeutic option in the vast majority of these patients at high risk of recurrent VTE with more concerns raised in high-risk APS patients and these deficient in protein S (PS). Adherence to DOACs is of paramount importance in these patients. In this review we presented available data on the management of patients with thrombophilia using rivaroxaban, dabigatran or apixaban at standard doses. Moreover, we also demonstrated the overall effects of DOACs on coagulation tests, particularly those determined during thrombophilia screening such as lupus anticoagulant, antithrombin, protein C, PS, activated protein C ratio. Despite the paucity of data from randomized studies, the current evidence supports the use of DOACs in thrombophilia, especially those who prefer such treatment or have unstable anticoagulation with vitamin K antagonists or unacceptable adverse events while using these drugs (**Adv Clin Exp Med 2016, 25, 6, 1321–1330**).

Key words: thrombophilia, antiphospholipid syndrome, anticoagulant drugs.

Direct oral anticoagulants (DOACs) or non-vitamin K oral anticoagulants (NOACs) are approved for stroke prevention in patients with non-valvular atrial fibrillation (AF) and therapy of venous thromboembolism (VTE) encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE) [1–3]. The DOACs currently available in Europe include 3 direct factor Xa inhibitors, rivaroxaban, apixaban and edoxaban, and 1 direct thrombin inhibitor, dabigatran. In Poland, rivaroxaban, apixaban and dabigatran are currently being used (Table 1).

DOACs offer a number of advantages over vitamin K antagonists (VKAs) such as a predictable dose response, fewer drug and food interactions, and no need for laboratory monitoring of the international normalized ratio (INR) or other coagulation tests [3]. Based on randomized controlled trials on DOACs in DVT or PE patients, the newer anticoagulants have been convincingly demonstrated to be at least as effective as the conventional treatment with low-molecular-weight heparins (LMWH) followed by VKAs in preventing recurrent VTE [4, 5].

In a pooled analysis of the 6 phase 3 trials, recurrent VTE and VTE-related deaths occurred in 2.0% of patients receiving DOACs compared with 2.2% of those given VKAs (relative risk [RR] 0.90, 95%

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Table 1. Characteristics of dabigatran, rivaroxaban and apixaban (reprinted with permission from Undas et al. [12], modified)

Variable	Warfarin	Dabigatran etexilatea	Rivaroxaban	Apixaban
Mode of action	↓ synthesis vitamin K-dependent coagulation factors	direct selective and reversible thrombin inhibitor	direct selective and reversible activated factor X inhibitor	direct selective and reversible activated factor X inhibitor
Time to peak plasma concentration	90 min (peak action after 4–5 d)	0.5–2 h	2–4 h	1–4 h
Half-life	36–42 h	12–14 h	5–9 h (young) 11–13 h (age > 65 years)	8–13 h
Substrate of P-glycoprotein transporter	no	yes	yes	yes
Substrate of CYP enzymes	yes (CYP3A4, CYP2C9)	no	yes (CYP3A4/5, CYP2J2)	yes (CYP3A4, CYP2C9)
Route of elimination	various	80% renal	66% renal (33% unchanged)	25% renal
Protein binding	99%	35%	90%	90%
Basic daily dose in AF	~5 mg (1–18 mg) target INR, 2–3	2 × 150 mg	1 × 20 mg	2 × 5 mg
Reduced daily dose	not applicable	2 × 110 mg	1 × 15 mg	2 × 2.5 mg

confidence interval [CI]: 0.77–1.06). For acute VTE treatment, the DOACs are non-inferior to well-managed VKA therapy [5]. Importantly, there was overall a 40% reduction in the risk of major bleeding in patients receiving DOACs with lower risks of intracranial bleeding (63% relative reduction), fatal bleeding (64% relative reduction), and clinically relevant non-major bleeding (27% relative reduction) [4]. With similar efficacy, better safety and the convenience of fixed dosing, guidelines now recommend the DOACs over VKAs for VTE treatment in patients without active cancer [5]. Appropriate anticoagulation in VTE patients reduces the risk of recurrent VTE, including life-threatening PE, and postthrombotic syndrome [6, 7].

Inherited Thrombophilia

Natural anticoagulant deficiencies (protein C, PC, or protein S, PS, or antithrombin, AT), homozygous factor V Leiden (FVL) and prothrombin G20210A, or combined defects, result in a severe thrombophilia phenotype, which occurs in approximately 4% of patients with idiopathic VTE [8]. Less commonly inherited thrombophilia is observed in patients with myocardial infarction or ischemic stroke [9].

In everyday practice VKAs are preferred in the therapy of VTE associated with thrombophilia. The prevalence of known thrombophilia in the VTE trials with DOACs ranged from 2 to 18% [10]. To our knowledge, only the data for thrombophilic patients with acute VTE participating in the RECOVER I and RECOVER II studies that assessed the efficacy and safety of dabigatran (150 mg bid) administered for 6–36 months were published as an abstract [11]. Thrombophilia was determined in 34% of the VTE patients yielding positive results in 24% of the cases, with no differences between dabigatran- and warfarin-treated individuals with FVL, prothrombin 20210A variant, deficiencies in AT, PC or PS as well as lupus anticoagulant (LA) or anticardiolipin antibodies. No differences in the efficacy or safety of dabigatran use depending on the thrombophilic factors were observed; however, dabigatran was used in as few as 11 AT deficient patients and 25 with PC or PS deficiency. The combined defects or homozygous mutations were not reported [12]. Below we present patients with severe inherited thrombophilia who were treated with DOACs and were reported in the literature.

Antithrombin Deficiency

Inherited AT deficiency is an autosomal dominant disorder with prevalence in the general population estimated between 1 : 500 and 1 : 5000 [13, 14]. This abnormality is diagnosed in 0.5–4.9% of patients after the first incident of VTE. In Poland, several AT deficient patients with VTE have been reported since 2011 [15–20]. There is

a 50-fold increased risk of VTE in AT deficient individuals [21, 14]

Experience with DOACs in AT deficiency is very limited. Cases of a 49-year-old male with AT deficiency and Crohn disease who was successfully treated with apixaban for 9 months and a 12-year-old girl with heparin-resistant severe thrombosis due to AT deficiency (homozygous AT Budapest III) treated with rivaroxaban have been published recently [22, 23]. DOACs that act directly without the participation of AT may represent a particularly attractive anticoagulant alternative to LMWH in AT deficient patients with a marked resistance to these agents [23]. Taken together, most AT deficient patients can be successfully treated with DOACs.

Protein C Deficiency

The prevalence of PC deficiency is estimated at 0.2–0.3% in the European population and 3% of patients after the first VTE [24]. We characterized genetically the first two Polish patients with PC deficiency [25, 26]. There is about a 10-fold increased risk of VTE in PC deficient subjects [14, 21].

Little is known about the efficacy of DOACs in PC deficient patients. Protein C deficiency complicated with warfarin-induced skin necrosis was successfully treated with dabigatran at standard doses [27]. In an 18-year-old woman with two PC mutations and the PC level of 3% warfarin therapy was changed to rivaroxaban with the subsequent increase of PC levels to 12–18%, but after missing two doses of rivaroxaban she developed upper limb DVT [10].

Protein S Deficiency

The prevalence of PS deficiency is estimated at 0.5% in Europe and at 2–12% among patients after the first incident of VTE [24, 28]. The Polish patients with this thrombophilia genetically characterized have been described recently [29–31, 32]. There is a 10-fold increased risk of VTE in PS deficient subjects [14, 21].

We showed recurrent VTE in two type 1 PS deficient patients with low free PS, below 20% of the reference range, who were treated with rivaroxaban, suggesting that this thrombophilia could be a risk factor for recurrent VTE on rivaroxaban [33]. In a 6-year-old child with severe homozygous PS deficiency rivaroxaban 40 mg/d was reported to be effective, indicating that higher doses of rivaroxaban are needed at low PS levels to protect against recurrent VTE [32].

Factor V Leiden and Prothrombin 20210A Mutation

The most common thrombophilia in Caucasians is FVL mutation that occurs in 5% of Caucasians and 3–7 times more commonly in patients with VTE. There is a 80-fold increased risk of VTE in homozygous FVL carriers [14, 21]. Prothrombin G20210A polymorphism, the second most common heritable thrombophilia, occurs in 3% of Europeans and is associated with similar VTE risk [14].

To our knowledge, the only report on the use of DOACs in FVL has described left ovarian and renal vein thromboses in a 30-year-old woman homozygous for FVL, taking combined oral contraceptives, which were successfully treated with rivaroxaban 20 mg/d [34]. Recently, acute myocardial infarction in a 65-year-old man receiving rivaroxaban following idiopathic PE associated with heterozygous prothrombin 20210A mutation has been reported [35]. Most experts consider DOACs as a safe and effective option for patients with heterozygous variants of these polymorphisms and likely for the majority of homozygous patients.

Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) is an autoimmune acquired disease associated with venous or arterial thrombosis and recurrent miscarriages [36–38]. The diagnosis of APS is based on the clinical presentation and 2 positive measurements of IgG or IgM antibodies against cardiolipin (aCL), β2 glycoprotein I (aβ2GPI), or LA. Young patients with VTE or ischemic stroke of unknown cause should be tested for APS [39]. The standard treatment for patients diagnosed with APS is bridging anticoagulation with heparins followed by VKA [36].

There have been a few case reports suggesting that DOACs, compared with VKAs, are less beneficial in patients with triple-positive APS, especially associated with a stroke, who received dabigatran and rivaroxaban [3, 4]. Despite these reports, some experts have recommended NOACs as an alternative to VKAs in the prevention of VTE in APS [11]. In 2015 we published a case series involving 12 patients with APS treated with rivaroxaban with 2 recurrent DVT episodes [40]. Jolland et al. [22] and Delgado et al. [41] demonstrated single cases of patients with APS receiving rivaroxaban who experienced a thrombosis relapse. Signorelli et al. [42] have presented 8 patients with

APS treated with rivaroxaban who experienced thrombosis recurrence, including 5 patients with triple positivity and 2 subjects with previous arterial thrombosis. On the other hand, several reports indicated good efficacy of DOACs in APS even with no or only one thrombotic relapse during follow-up [43, 44].

Sciascia et al. [10] summarized observational studies regarding the use of DOACs in APS published till the end of 2015 (n = 87) and showed relatively good clinical outcomes in patients with APS on DOACs during follow-up up to 29 months. Betancur et al. [45] reported cases of fully successful prevention of VTE recurrence in 7 patients treated with rivaroxaban and a single individual on apixaban.

The recurrence rate of thrombosis on DOACs observed in available studies is similar to that reported by Cervera et al. [46], who demonstrated 25% recurrence of thrombosis within the 5 years period in patients with APS mostly treated with anticoagulants. Many experts consider DOACs as a valuable therapeutic option in APS patients who initiate anticoagulant therapy or prefer such agents over VKAs [33]. Other experts are cautious and repeat that VKAs remain to be the mainstay treatment for thrombotic APS, unless they refuse to undergo such inconvenient treatment or suffer from adverse events [42].

An open-label, randomized, controlled trial – rivaroxaban in antiphospholipid syndrome (RAPS) study, performed on thrombotic APS patients allocated to warfarin or rivaroxaban 20 mg daily, was published in September 2016 [47]. The primary endpoint, the percentage change in endogenous thrombin potential (ETP) from randomization to day 42, was higher in the rivaroxaban group together with markedly lower peak thrombin generation, the most sensitive marker of thrombin formation. No VTE episodes or serious bleeding were reported, leading to the conclusion that rivaroxaban "could be an effective and safe alternative" in thrombotic APS [47]. Although the size of the study groups was limited and the observation period short, the RAPS study provided valuable confirmation that the impact of rivaroxaban on blood coagulation is comparable to warfarin with a target INR of 2.5 in patients with various forms of APS.

Own Recent Experience with DOACs in Thrombophilia

Recently, we have analyzed 33 adult patients with severe thrombophilia aged 19–64 years, who had been switched from warfarin or acenocoumarol to DOACs [A. Undas, unpublished data]. This group included 5 (15%) patients deficient in AT, 3 (9%) deficient in PC, 4 (12%) deficient in PS, 1 (3%) homozygous FVL mutation carrier, 3 (9%) carriers of homozygous PT G20210A mutation and most with combined defects. As few as 3 cases of recurrent VTE on DOACs were recorded during the follow-up up to 32 months with no fatalities [A. Undas, unpublished data]. In our experience, PS deficiency appears to be related to the increased risk of VTE recurrence, which was observed in 2 of the 3 patients who experienced recurrent VTE on DOACs. It has been suggested, however, that various genetically determined thrombophilias could affect differently the effect of DOACs [43].

Our recent analysis of 56 consecutive patients with APS aged 23 to 64 years, including 16 (28.6%) with triple positive APS, who were treated with DOACs supported the concept of satisfactory efficacy and safety of DOACs, mainly rivaroxaban, in this thrombophilia. During follow-up up to 43 months, 6 (2.98% per year) patients, including 4 subjects with triple positive APS, experienced recurrent nonfatal thromboembolic events, including 1 myocardial infarction and in 2 cases nonadherence was observed before the recurrences [A. Undas, unpublished data].

Effect of DOACs on Routine Coagulation Tests

The impact of DOACs on the laboratory assays depends on the type of the drug, the drug concentrations, the assay, reagents and instruments used to test the sample [48]. Assays based on thrombin are more affected by direct thrombin inhibitors, whereas direct FXa inhibitors influenced much more FXa-based methods. The blood levels connected with DOACs vary from a few ng/mL prior to drug administration ("trough"), to several hundred ng/mL, if the sample is taken 2–4 h after the drug's intake ("peak") (Table 2). The first Polish experience with determining dabigatran and rivaroxaban in the circulating blood was published in 2014 [49–51]. Table 3 shows the effects of DOACs on coagulation assays.

The presence of rivaroxaban in blood results in the prolongation of prothrombin time (PT) in a manner dependent on the concentration of the drug, while apixaban has little effect on the PT [52]. Rivaroxaban also alters thromboelastographic parameters [53]. For rivaroxaban, the concentration of the drug required to double the clotting time (CT) may range from 498 to 591 ng/mL using Quick-type PT assays in comparison to at least 1300 ng/mL when tested using Owren-type PT as-

Table 2. Concentrations of direct oral anticoagulants based on [57, 62, 76, 77, 78]

Parameter	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Peak*	64–223 (150 mg/bid)	91–195 (10 mg/od)	36–100 (2.5 mg/bid)	376–421 (30 mg/od)
		160–360 (20 mg/od)	122–412 (10 mg/bid)	388–444 (60 mg/od)
Trough*	31–225 (150 mg/bid)	1–38 (10 mg/od)	20–94 (2.5 mg/bid)	130–174 (30 mg/od)
		4–96 (20 mg/od)	30–412 (10 mg/bid)	268–336 (60 mg/od)

* values in ng/mL for peak and trough are expressed as 5^{th} – 95^{th} percentile ranges (dose/bid – twice daily, od – once daily).

says [54]. Apixaban concentrations that ranged from 480 to > 1000 ng/mL led to double the PT with the 10 different reagents [55]. It has been observed that the TriniCLOT Excel S of the PT reagents show a dose-dependent response to apixaban across the 0–500 ng/mL range [56].

Increased dabigatran concentrations prolonged PT, but the correlation is poor [57]. The Owren-type PT may be normal in up to about ¾ samples with dabigatran of 40 ng/ml or above [58]. The PT is not recommended to quantify or even detect dabigatran [59].

Activated partial thromboplastin time (APTT) could be useful to determine the anticoagulant activity of dabigatran. The presence of dabigatran in plasma results in the prolongation of the APTT in a concentration- and a reagent-dependent manner [60, 61]. Samples containing dabigatran in the amount of 120 ng/mL tested using different APTT reagents may give results from 26 to 92 s [62]. The correlation between dabigatran and the APTT is curvilinear. Linear dose response is followed by flattening at about 300 ng/mL [62]. The percentage of normal APTT samples with dabigatran concentrations of 40–160 ng/mL may reach 26% [58]. The APTT was always prolonged when dabigatran concentrations exceeded 160 ng/mL [58]. Dabigatran may induce hypercoagulable effects by inhibiting thrombomodulin-mediated activation of protein C, which may be the cause of normal APTT in individuals with high dabigatran concentrations [58].

The APTT demonstrates a concentration-dependent prolongation in a nonlinear manner in response to direct FXa inhibitors in samples, although to a lesser extent than to dabigatran [48, 63–65]. APTT reagents are much more sensitive to rivaroxaban and edoxaban than to apixaban [52]. Clotting time of apixaban enriched (100 ng/mL) samples was prolonged only 1.1 times compared with the control, when measured using 10 different APTT reagents [62]. Double CT was obtained at rivaroxaban concentrations and ranged from 330 to 637 ng/mL depending on the reagent [56]. The reasons for a much weaker PT and APTT response to apixaban compared to rivaroxaban are not known [56], and the phospholipid composition of the reagents may contribute to this observation [66].

Thrombin time (TT) is very sensitive to dabigatran, and low concentrations of 25 ng/mL may render the tested plasma samples unclottable [60, 65]. A normal standard TT can exclude the presence of dabigatran in a sample [67]. Dabigatran can be quantified using a chromogenic ecarin assay, ecarin clotting time or a modified (dilute) TT, where excessive sensitivity is overcome by lower concentrations of heparin or sample dilution [60, 68]. Since FXa is not involved in fibrinogen conversion into fibrin, the TT is not affected by direct FXa inhibitors [48, 64].

Effect of DOACs on Results of Thrombophilia Testing

Lupus Anticoagulant

Lupus Anticoagulant (LA) is detected using assays based on APTT or Russel's viper venom time (RVVT) containing reagents with low (screening reagents) and high (confirmation reagents) phospholipid concentrations. LA prolongs clotting time using screening reagents much more than when using confirmation reagents. Both APTT- and RVVT-based assay are affected by DOACs. It was shown that dabigatran prolongs the RVVT in an almost linear manner, although the correlation was not potent [58]. The RVVT is sensitive to low concentrations of dabigatran. Dabigatran concentrations below 40 ng/mL prolong the RVVT in 72% of plasma samples [58].

Table 3. Effects of direct oral anticoagulants on coagulation assays

Test	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
PT	↑	↑↑↑	↑	↑↑↑
APTT	↑↑↑	↑↑	↑	↑↑
Thrombin time	↑↑↑↑↑	–	–	–
Reptilase time	–	–	–	–
Fibrinogen Clauss method PT-derived	 ↓ (↓) (↑)	 – ↑	 – (↑)	 – (↑)
Antithrombin based on FXa inhibition based on FIIa inhibition	 – ↑	 ↑ –	 ↑ –	 ↑ –
RVVT	↑	↑↑↑	↑↑	↑↑
Protein C clotting assay chromogenic assay	 ↑↑ –	 ↑ –	 (↑) –	 ↑ –
Protein S clotting assay free protein S antigen (immunologic)	 ↑↑ –	 ↑↑ –	 ↑ –	 ↑ –
Activated protein C resistance (ratio) based on APTT based on RVVT based on prothrombinase activation	 ↑↑ (↑)	 ↑ (↑) –	 ↑	 ↑
Anti-FXa	–	↑↑↑↑	↑↑↑↑	↑↑↑↑
Ecarin clotting time	↑↑	–	–	–
Intrinsic coagulation factors (VIII, IX, XI, XII) based on APTT chromogenic FVIII	 ↓↓ –	 ↓ ↓	 ↓ ↓	 ↓
Extrinsic coagulation factors (II, V, VII, X) based on PT	 ↓	 ↓↓	 ↓↓	 ↓↓
D-Dimer	–	–	–	–
LA (ratio) based on APTT based on RVVT	 ↑↑ ↑↑	 ↑↑ ↑↑	 ↑	 ↑↑

APTT – activated partial thromboplastin time; FIIa – thrombin; FXa – active factor X; PT – prothrombin time; RVVT – Russel's viper venom time (in parentheses – a possible effect of DOACs).

Rivaroxaban prolongs much more the RVVT using reagents with small phospholipid content compared with apixaban, while there is no difference in the RVVT if reagents with high phospholipid content are used. Thus, a false positive LA may be obtained for rivaroxaban at 100 ng/mL and apixaban at 600 ng/mL [66]. We confirmed that to reliably evaluate LA in VTE patients on rivaroxaban, blood should be taken at least 24 h after the last drug administration [69]. It has been recommended that the LA testing should be performed 2–3 days after the last dose of DOACs [71].

Activated Protein C Resistance (APCR)

The ratio below about 2.0 of APTT or RVVT with and without added exogenous activated protein C (APC) indicates FVL mutation. Assays based on APTT or prothrombinase are affected by dabigatran at a concentration of 50 ng/mL and more [72]. Our data indicates that rivaroxaban, at least in the therapeutic range of concentrations, does not affect APC-R testing using the

ProC Ac R RVVT-based assay [70]. This test could be recommended if the time from the last dose of DOACs is uncertain or unknown. The influence of rivaroxaban on an APTT-based assay results in an increased APCR ratio. Assays based on prothrombinase activation exhibit less sensitivity to rivaroxaban and a smaller increase in the APCR ratio when concentrations of rivaroxaban increase [54]. Genetic testing is the reliable method to confirm FVL in patients on DOACs.

Antithrombin

Dabigatran alters thrombin-based chromogenic assays leading to overestimated results of AT levels, whereas FXa-based assays are unaffected by this drug [73]. Estimations of the increase in AT activity yield falsely elevated results, i.e., by 12% per 200 ng/mL of dabigatran [72]. A factitious increase in AT activity at 250 ng/mL dabigatran ranged from 15 to 21% depending on the reagent [61]. On the other hand, direct FXa inhibitors influence significantly the FXa-based assays, and, for example, rivaroxaban at 290 ng/mL can cause an overestimation of AT activity up to 44% [61].

Protein C

Dabigatran affects the clot-based assays leading to overestimated PC levels. The most commonly used assay for PC deficiency screening is not influenced by DOACs. The same holds true for antigen assays to determine PC [73].

Protein S

Results of PS testing in the presence of dabigatran with any of the clot-based assays (APTT, PT, RVVT or FXa) can be falsely increased, while PS antigen assays are unaffected [73]. The PS activity assays are also influenced by rivaroxaban in a reagent-dependent manner. Mean activity of samples spiked with rivaroxaban of 200 ng/mL was 174% using the PT-based method, while for RVVT- and APTT-based assays mean activities were 119 and 99%, respectively [74].

Summary

Little is known about the efficacy and safety of DOACs in real-life patients diagnosed with severe inherited thrombophilia and APS. For this reason, the unlimited use of DOACs in patients with such thrombophilia is now controversial for many clinicians. On the other hand, given the lack of anticoagulation clinics in Poland, the burden of lifelong anticoagulant treatment with VKAs is large and this situation encourages numerous patients to seek a transition to DOACs, even if the monthly cost of such therapy is considerable. Moreover, manufacturers of DOACs do not discourage clinicians from using this class of drugs in thrombophilic patients and in none of the VTE trials with DOACs was severe thrombophilia an exclusion criterion. It has been postulated that "While it is possible the DOACs may be a viable option for VTE treatment in patients with weaker underlying thrombophilias (e.g., heterozygous FVL), caution or avoidance, especially in highly pro-thrombotic states such as APS or heparin-induced thrombocytopenia, is suggested until further evidence becomes available" [75]. Based on the current literature and our experience, we postulate using DOACs in thrombophilic patients initiating anticoagulant therapy and in those who prefer such a therapy or have unstable therapy with VKA. While performing a diagnostic evaluation for thrombophilia with the use of coagulation tests in patients receiving DOACs, at least 24 h interval between the drug's intake and blood collection should be confirmed, especially at the LA testing, which may require the interruption of the administration of DOACs for a period of 2–3 days. Such a procedure should be performed not earlier than after 3–6 months after the VTE event. The measurement of DOACs levels in the samples tested may help interpret the results. Taken together, growing evidence indicates that DOACs are a valuable and promising therapeutic option in the therapy of acute VTE as well as in secondary prevention of thrombotic events in individuals suffering from APS or inherited thrombophilic disorders. It should be highlighted that successful and safe treatment in this high-risk population with DOACs requires good compliance and adherence.

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